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U.S. Environmental Protection Agency guidelines for carcinogen risk assessment: Past and future [1]

Jeanette Wiltse, Vicki L. Dellarco *

National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC, USA

Abstract

The U.S. Environmental Protection Agency (USEPA) recently proposed new guidelines to update and replace the 1986 USEPA *Guidelines for Carcinogen Risk Assessment*. Today, there is a better understanding of the variety of modes by which carcinogens can operate that did not exist when the 1986 USEPA guidelines were published. Many laboratories are adding new test protocols in their programs directed at questions concerning the mechanisms of action of carcinogens. In response to the evolving science of carcinogenesis, the new guidelines provide an analytical framework for incorporating all relevant biological information and recognizing a variety of situations regarding cancer risk. In addition, the guidelines are flexible enough to allow consideration of future scientific advances.

Keywords: Risk assessment; Cancer; Carcinogen

1. Introduction

Risk assessment is an integral element of environmental decision making. It is organized by the paradigm put forward by the National Academy of Sciences/National Research Council (NAS) and based on analyses of scientific data to determine the likelihood, nature and magnitude of harm to public health associated with exposure to environmental agents (NRC, 1983, 1994). The NAS paradigm defines four types of analysis: hazard assessment – does the chemical produce adverse health effects?; dose-response assessment – how does the frequency of adverse effects change with dose?; and exposure assessment – to how much chemical are humans exposed in various environments, and what are the conditions of exposure?; and risk characterization. Risk characterization, the fourth element of the paradigm, is the final analysis that summarizes and integrates the scientific findings of the hazard, dose-response, and exposure assessments to present the overall conclusions about potential human risk along with the strengths and weaknesses of the evidence so that decision makers can understand and use the information effectively.

Risk assessment guidelines encourage consistency

* Corresponding author. U.S. Environmental Protection Agency, National Center for Environmental Assessment (8601), 401 M St., S.W., Washington, DC 20460, USA. Tel.: (202) 260-7336; Fax: (202) 260-0393; E-mail, dellarco.vicki@epamail.epa.gov

[1] Although this paper has been subjected to review and approved for publication, it does not necessarily reflect the views and policies of the U.S. Environmental Protection Agency. The opinions expressed within this paper reflect the views of the authors.

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in procedures to support decision making across the many different U.S. Environmental Protection Agency (USEPA) regulatory programs. The USEPA has published several risk assessment guidelines (i.e., cancer, mutagenicity, neurotoxicity, developmental and reproductive toxicity, exposure, and complex mixtures) to provide staff and decision makers with guidance and perspectives necessary to develop and use risk assessments (USEPA, 1986a,b,1991a,1992, 1993, 1994a).

Risk assessment guidelines are viewed as living documents that should keep pace with advances in science. Toward this end, USEPA has proposed revised guidelines for carcinogen assessment to accommodate the current understanding of carcinogenesis and the new technologies being employed in toxicology (USEPA, 1996). These new guidelines stress the understanding about how an agent induces tumors (i.e., mode of action) in determining and estimating human cancer risk. The emphasis on use of mode of action and toxicokinetic information is to reduce the uncertainties associated with extrapolations from high doses to low doses, from one route of exposure to another, and from experimental animals to humans. Also, an understanding of an agent's mode of action will begin to break down the dichotomy between the quantitative approaches for cancer and noncancer risks. The underlying bases for certain noncancer toxicities and cancer may have several commonalities. For example, chemically induced toxicity can cause cell death. Surviving cells may then compensate for that injury by increasing cell proliferation (hyperplasia), which may underlie many types of toxic responses. If this proliferative activity continues unchecked, it may result in tumors. Thus, the same basic toxic mechanisms may be related to the cancer outcome and to other types of toxic effects.

This article discusses the proposed revisions to the 1986 USEPA *Guidelines for Carcinogen Risk Assessment* (USEPA, 1986a). It should be stressed that the USEPA's 1996 proposed guidelines are undergoing public comment, and changes could result in what is described in this paper (USEPA, 1996). This discussion is oriented toward readers of *Mutation Research*. Although the basic organization and certain key aspects of the new guidelines are covered, they are not discussed in detail. Interested readers may obtain a copy of the proposed guidelines [2] (USEPA, 1996).

2. Framework of the 1986 USEPA *Guidelines for Carcinogen Risk Assessment*

The USEPA's involvement in cancer risk assessment spans approximately 20 years. In 1976, the USEPA first published interim guidelines for cancer risk assessment (USEPA, 1976). These guidelines were updated in 1984 and finalized in 1986 (USEPA, 1986a). Since their publication, the USEPA has recognized the need to revise and reconsider the 1986 guidelines. Thus, revisions to the 1986 guidelines have been many years in the making. The 1996 proposed guidelines are the result of a number of USEPA-sponsored workshops (e.g., USEPA, 1994b), recommendations from the National Academy of Science/National Research Council report on *Science and Judgment in Risk Assessment* (NRC, 1994), and extensive USEPA and federal reviews. To understand the need for revision, it is useful to discuss the framework and weight-of-evidence process of the 1986 guidelines.

2.1. 1986 Weight-of-evidence process

In the 1986 guidelines, hazard identification and the weight-of-evidence process focus on tumor findings. The human carcinogenic potential of agents is characterized by a six-category alphanumeric classification system: A, human carcinogen (sufficient human evidence); B1, probable human carcinogen (limited human evidence); B2, probable human carcinogen (sufficient animal evidence); C, possible human carcinogen (limited animal evidence); D, not classifiable; and E, evidence of noncarcinogenicity. As illustrated in Fig. 1, the weight-of-evidence ap-

[2] The USEPA *Proposed Guidelines for Carcinogen Risk Assessment* is available on the Internet (http://www.epa.gov/ORD). To obtain a 3.5 inch disk in WordPerfect 5.1 format, contact ORD Publications, Technology Transfer and Support Division, National Risk Management Laboratory, U.S. Environmental Protection Agency, 26 W. Martin Luther King Drive, Cincinnati, OH 45268, USA.

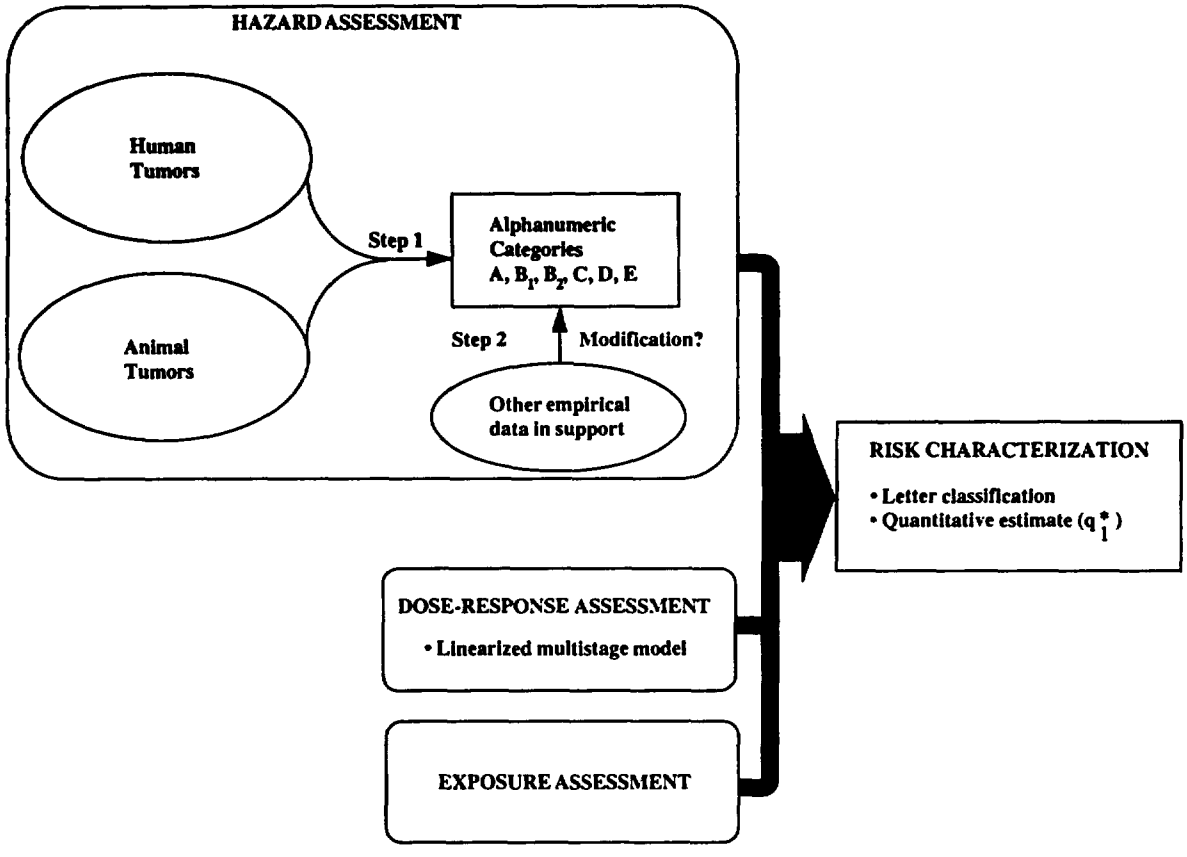

Fig. 1. The framework of the USEPA 1986 *Guidelines for Carcinogen Risk Assessment*. The 1986 guidelines are organized on the paradigm put forth by the National Academy of Sciences (NRC, 1983), which includes four components of analysis: hazard, dose-response, and exposure assessments and risk characterization. The weight-of-evidence process used for determining cancer hazard primarily focuses on tumor findings. The hazard and dose-response analyses are done separately of each other.

proach for making judgments about cancer hazard analyzes human and animal tumor data separately, then combines them to make the overall conclusion about potential human carcinogenicity. The next step of the hazard analysis is an evaluation of supporting evidence (e.g., mutagenicity, in vitro cell transformation) to determine whether the overall weight-of-evidence conclusion should be modified.

2.2. 1986 Dose-response approach

The dose-response assessment component is separate from hazard assessment. The 1986 guidelines call for the most appropriate extrapolation model but give no guidance in choosing such a model. It is simply stated that if there is limited information and the understanding of mechanisms is not sufficient to choose a particular model, then a default approach based on the assumption of low-dose linearity should be used by applying the linearized multistage (LMS) procedure, which extrapolates risk as the 95% upper-bound confidence interval. This linear default position is, in part, based on the belief that the process of cancer induction is similar among chemicals, namely electrophilic reaction of carcinogens with DNA, causing mutations that are essential elements of the carcinogenic process. Additivity to background (i.e., the agent acts additively with an already ongoing process) also is referred to in support of the assumption of low-dose linearity (USEPA, 1986a; Krewski et al., 1995). The LMS model is the only dose-response default for extrapolation in the 1986 guidelines.

3. Limitations of the 1986 guidelines approach

Because the alphanumeric classification system relies primarily on tumor findings, full use of all physical, chemical and biological data relevant to induced carcinogenesis is not explained adequately or promoted. Thus, 'supportive' data have come into play in classifying the cancer potential of an agent for human beings in fewer instances than may be desirable. Moreover, the conditions of hazard expression (e.g., route, duration, pattern, or magnitude of exposure) are not conveyed with the 1986 letter classification system. This is a notable shortcoming, because it is clear that some carcinogens may pose a risk by one route of exposure but little or no risk by another exposure route. For example, it has been reported that inhaled vinyl acetate (600 ppm) produces a statistically significant increase in tumors (nasal) in rats but when given by drinking water, a statistically significant increase in tumor response was not reported (Bogdanffy et al., 1994b,c).

Because the 1986 guidelines do not promote the full use of information on mechanisms in the hazard assessment, the dose-response assessments are based on modeling tumor data with the LMS approach. Although the 1986 guidelines do not discourage departure from defaults, this has been rare in practice. There is, however, an increasing number of cases, where mode of action data play a prominent part in USEPA cancer risk assessments, such as hormone imbalance and thyroid gland neoplasia, alpha$_{2\mu}$-globulin and renal neoplasia in the male rat, and receptor binding and dioxin carcinogenesis (Hill et al., 1989; USEPA, 1991b,1994c).

The 1986 guidelines provide very little direction for risk characterization, and thus in practice, risk characterization boiled down to a letter category of risk and a quantitative risk estimate (i.e., q_1 * slope factor). Today, there is a great deal of emphasis on incorporating and improving the risk characterization component of health risk assessments (NRC, 1994, USEPA, 1995).

4. Understanding of carcinogenesis

Our understanding of carcinogenesis has greatly advanced since publication of the 1986 *Guidelines for Carcinogen Risk Assessment*. Over the past decade, research in cancer biology has provided the opportunity to look beyond traditional approaches for assessing cancer risk. There have been significant gains in understanding not only the genes involved in controlling normal cell growth, programmed cell death, and cellular differentiation, but the changes in these genes that become essential elements of the carcinogenic process (e.g., Hsu et al., 1991; Bottaro et al., 1991; Varmus and Weinberg, 1993). Since publication of the 1986 guidelines, research has revealed a variety of modes by which carcinogens can operate (Barrett, 1993; Cohen and Ellwein, 1991; Hill et al., 1989; USEPA, 1991b,1994c). Carcinogenesis can be induced by both mutagenic and nonmutagenic agents, including agents that directly interact with and damage DNA, agents that cause loss of heterozygosity by mechanisms other than direct DNA reactivity, and agents that operate through epigenetic or nonmutagenic mechanisms (e.g., receptor-mediated pathways, hormonal or physiological disturbances).

Rapidly advancing molecular technologies are providing the tools that permit a more detailed understanding of the carcinogenic process (i.e., chemical and gene interactions) and providing mechanistically based approaches for testing chemicals. Many laboratories are adding new test protocols in their programs directed at questions of mode of action (Tennant et al., 1995, 1996).

5. Framework of the *1996 Proposed Guidelines for Carcinogen Risk Assessment*: major changes from the USEPA 1986 guidelines

The 1996 proposed guidelines include a number of changes that address the limitations of the 1986 guidelines and accommodate new information on carcinogenesis. It should be noted that results of an assessment under the new guidelines will not differ greatly from those under the 1986 guidelines, unless new kinds of information are forthcoming from research on mechanisms and toxicokinetics. The basic analytical framework of the 1996 proposed guidelines as compared with the 1986 guidelines is discussed below.

5.1. Characterizations of hazard, dose response, and exposure

In its 1994 report about the use of science and judgment in risk assessment for hazardous air pollutants, the NAS/NRC recommended that the USEPA incorporate characterizations of risk that are both descriptive and mathematical in its risk assessment documents (NRC, 1994). In 1995, the USEPA also issued a policy statement and guidance for risk characterization (USEPA, 1995). In response, the structure of the 1996 proposed guidelines includes technical characterizations that are derived from the hazard, dose-response, and exposure assessments.

Technical characterizations are important components of the new guidelines and serve to explain the key lines of evidence and conclusions, discuss the strengths and weaknesses of the evidence, present alternative conclusions, and point out significant issues and uncertainties deserving serious consideration. As shown in Fig. 2, the three technical characterizations are integrated to form the overall synthesis and conclusions about human risk presented in the risk characterization summary.

5.2. Hazard assessment (weight-of-evidence process)

The hazard assessment component of the 1996 proposed guidelines places emphasis on using information about an agent's mode of action to reduce the uncertainty in describing the likelihood of harm and in identifying appropriate dose-response extrapolation approaches. This emphasis is based on the growing sophistication of research and testing methods. As shown in Fig. 3, the proposed guidelines call for a weight-of-evidence approach that considers all rel-

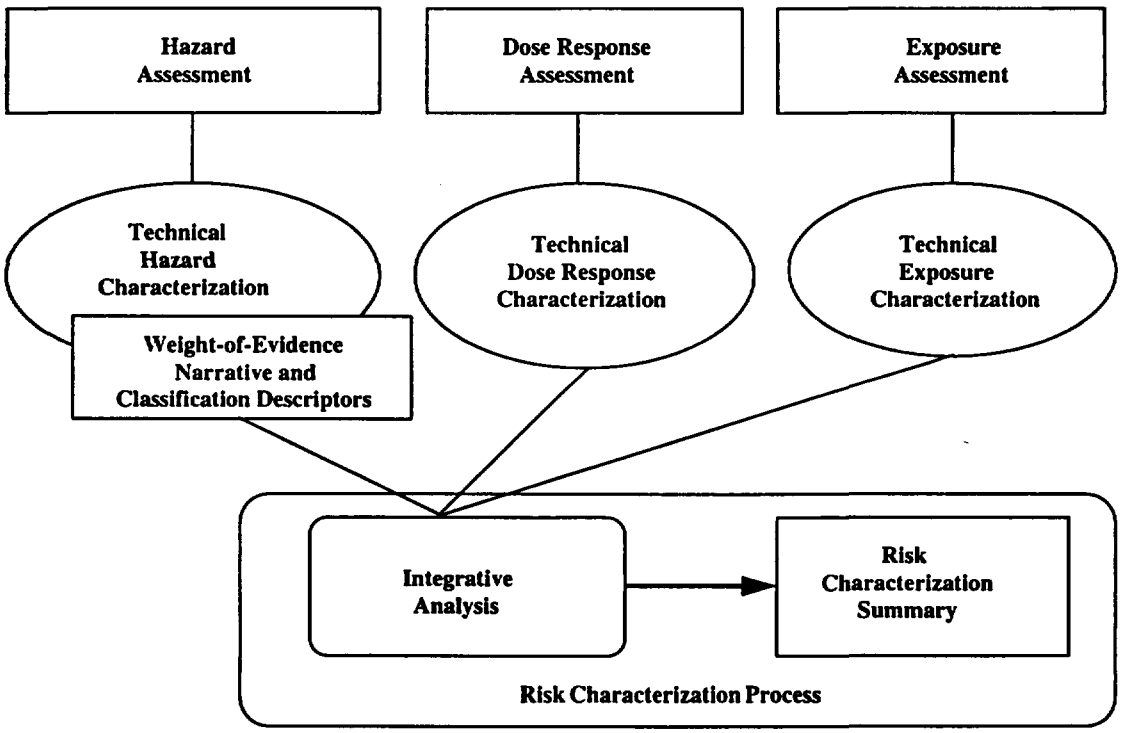

Fig. 2. The framework of the USEPA 1996 *Proposed Guidelines for Carcinogen Risk Assessment*. The 1996 guidelines are organized on the paradigm put forth by the National Academy of Sciences (NRC, 1983) and modified in 1994 (NRC, 1994). In this new structure there is an increased emphasis on discussing characterizations of hazard, dose-response, and exposure assessments. These technical characterizations serve to integrate the analyses conducted in these assessments, explain the weight of evidence and strengths and weaknesses of the data, and discuss issues and uncertainties that merit serious consideration. The technical characterizations themselves are integrated into the overall conclusions of risk, which are presented in the risk characterization summary that completes the risk assessment process.

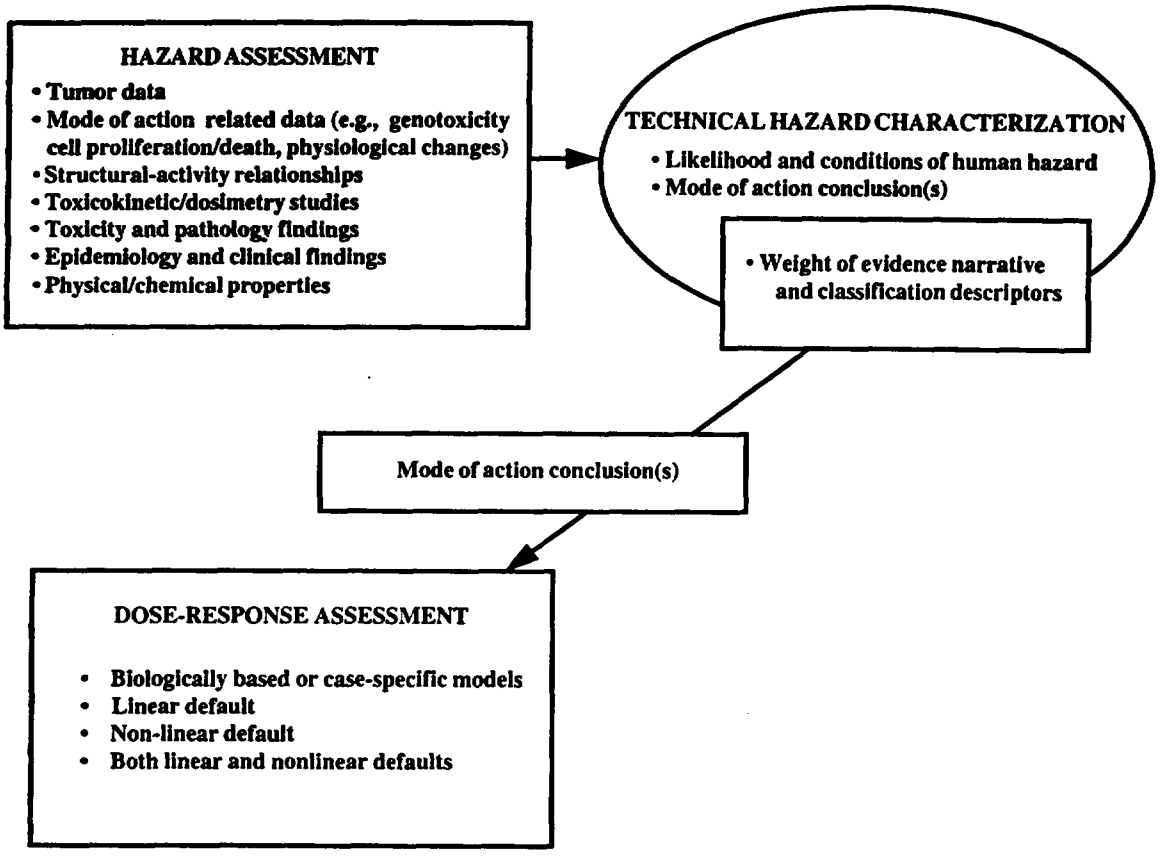

Fig. 3. The hazard, weight-of-evidence, and dose-response process of the USEPA 1996 *Proposed Guidelines for Carcinogen Risk Assessment*. The hazard and weight-of-evidence processes embrace an analysis of all relevant biological information and emphasize understanding the agent's mode of action in producing tumors to reduce the uncertainty in describing the likelihood of harm. The mode of action conclusions provide guidance in determining the most appropriate dose-response extrapolation procedures.

evant data in reaching conclusions about the potential human carcinogenicity of an agent. This a major change from the 1986 guidelines in which an interim classification of an agent was essentially driven by the tumor findings.

A technical hazard characterization is called for in the proposed guidelines to integrate the data analysis of all relevant studies into weight-of-evidence conclusions of hazard and to present the agent's mode of action (i.e., the agent's influence on molecular, cellular, and physiological functions) in producing tumors. Understanding the mode of action helps interpret the relevancy of experimental animal data and guides the most appropriate dose-response extrapolation procedure. The conditions (i.e., the route, duration, pattern, and magnitude of exposure) under which the carcinogenic effects of the agent may be expressed are also presented in the hazard characterization.

5.3. Weight-of-evidence narrative

A short weight-of-evidence narrative is derived from the technical hazard characterization. The narrative is intended for risk managers and other users, and it replaces the 1986 alphanumeric classification system. It briefly explains key data in common language, highlighting the significant strengths, weaknesses, and uncertainties of the main lines of contributing evidence. The conclusions about poten-

tial human carcinogenicity are presented by route of exposure, and the conditions of expression of carcinogenicity are discussed. The narrative recommends dose-response approaches based on the understanding of mode of action.

5.4. Classification descriptors

The weight-of-evidence narrative includes classification descriptors. Three standard categories of descriptors of hazard – 'known/likely,' 'cannot be determined,' and 'not likely' – replace the 1986 six letter categories (i.e., A–E). These descriptors are presented within the weight-of-evidence narrative to preserve the complexity associated with each data set on a given agent. Because of the wide variety of data sets encountered on agents, these descriptors are not meant to stand alone; rather, the narrative context is intended to provide a transparent explanation of the biological evidence and how the conclusions were derived. Subdescriptors within the categories are used to further refine the description of carcinogenic potential of an agent.

The 'known/likely' category includes agents for which adequate epidemiologic evidence (known) or a combination of epidemiologic and experimental evidence demonstrates an association between human exposure and cancer. Even in the absence of definitive epidemiologic evidence, agents can be considered 'as if known' human carcinogens if strong experimental evidence exists along with human data suggesting an association. The category also includes agents that produce tumors by modes of action that are relevant to humans can be judged 'likely' to produce cancer in humans based on experimental data including animal testing and mode of action information. In some cases, tumor data may not be available for an agent, but data on a structural analogue plus other key data may indicate that the agent of interest should be judged 'likely' to be carcinogenic to humans.

The 'cannot be determined' category includes agents for which tumor findings or other key data are suggestive, conflicting, or limited in quantity, and thus are not adequate to demonstrate convincingly the human carcinogenic potential of the agent. The rationale for why an agent falls in this category is to be given.

The 'not likely' category includes agents observed not to be carcinogenic in well-conducted studies in at least two appropriate species. Also, agents whose only carcinogenic effects are considered not relevant to humans (e.g., male rat kidney tumors due to accumulation of $alpha_{2u}$-globulin) would be considered 'not likely' to be human carcinogens. Unlike the 1986 classification scheme, use of descriptors enables communicating the conditions of cancer hazard within a narrative. Accordingly, a narrative could characterize an agent as 'not likely' below a certain dose range and 'likely' above that range, or 'not likely' to be carcinogenic by one route of exposure and 'likely' to be a human carcinogen by another route.

5.5. Mode of action information: role in dose-response assessment

It is the sum of the biology of the organism and the chemical properties of an agent that leads to an adverse effect. Thus, an evaluation of the entire range of data (i.e., physical, chemical, biological, and toxicological information) allows one to arrive at a reasoned judgment on an agent's mode of action and the selection of the most appropriate dose-response extrapolation procedure. Although cancer is a complex and diverse process, a risk assessment must operationally dissect the presumed critical events, at least those that can be measured experimentally, to derive a reasonable approximation of human risk. It is unrealistic to think that such approximations are perfect. Below is a brief discussion of some general considerations relevant to an understanding of the agent's mode of action and for selecting dose-response extrapolation procedures.

The ability of an agent to affect DNA remains an important aspect in cancer risk assessment. Cancer ultimately involves lesions (often multiple) occurring in genes that control cellular growth and differentiation (Williams et al., 1996). A large database exists on mutagenic substances known to produce tumors at multiple sites and in multiple species (Ashby and Tennant, 1991; Tennant et al., 1996). Further, an extensive review of the literature has revealed that alkylating agents produced tumors in Fischer 344 rats in a variety of tissues in addition to the sites of spontaneous tumors (Lijinsky et al., 1993). Thus, it

is reasonable to invoke a mutagenic mechanism for DNA-reactive agents as a contributing influence on the carcinogenic process. Finally, most known human carcinogens are DNA reactive (Shelby and Zeiger, 1990).

In cancer risk assessment, not only is it important to determine whether an agent is mutagenic, it is equally, if not more important, to have insight into mechanisms of mutagenesis, which may have different implications for the dose-response assessment. It is well known that many carcinogens are electropiles that interact directly with DNA, resulting in mutations. Not all mutagens, however, are directly DNA reactive. For example, some agents may induce mutations as a secondary consequence of other processes such as inhibition of apoptosis (Goldsworthy et al., 1996) or free radical generation (Clayson et al., 1994). Still others may produce mutations by interacting with non-DNA targets, such as inhibitors of topoisomerases, which are enzymes involved in the maintenance of DNA and chromosome segregation (Froelich-Ammon and Osheroff, 1995). Some agents have been shown to interfere directly with the mitotic spindle and result in numerical chromosomal anomalies (aneuploidy). Aneuploidy has been observed in the early stages of neoplastic transformation and as a nonrandom event in certain tumors (Barrett, 1992, 1993).

A variety of genetic alterations (e.g., point mutations, small and large deletions, amplifications, and chromosomal translocations, inversions and loss) have been observed in oncogenes and tumor suppressor genes (Williams et al., 1996). Specific genetic alterations have been associated with certain tumors such as Burkitt's lymphoma and translocations associated in the *c-myc* gene (Tucker and Preston, 1996). Some genetic alterations are one- event lesions (e.g., point mutations), whereas other genetic end points are two-event lesions (e.g., chromosomal inversions or translocations). Thus, different genetic lesions that influence the carcinogenic process may have different implications in the dose-response assessment.

Failure to detect genetic effects in standard tests may suggest that a carcinogen operates by another mechanism, and other molecular and cellular interactions or physiological disturbances need to be considered. It is possible for an agent to alter gene expression (transcriptional, translational, or post-translational modifications) by means not involving mutations (Barrett, 1992; Pitot, 1995). For example, perturbation of DNA methylation patterns may contribute to carcinogenesis (Goodman and Counts, 1993). Other mechanisms may involve cellular reprogramming through hormonal or receptor-mediated mechanisms (Ashby et al., 1994; Barrett, 1992; Pitot, 1995). Chemical interference with gap-junctional intercellular communication may be a contributing factor in tumor development (Yamasaki, 1996). Increased cell proliferation is an important element of carcinogenesis, and thus an understanding of the nature of the proliferative response is important (Cunningham, 1996). In addition to cellular and molecular studies, pathology and toxicology results, as well as clinical findings, may also provide important insights into an agent's mode of action.

In summary, an agent's ability to induce tumors is likely mediated by a number of different mechanisms (e.g., genetic, nonmutagenic, or epigenetic) at different steps of the carcinogenic process (Barrett, 1992). Regardless of the mechanisms, DNA is ultimately impacted. In any judgment about an agent's mode of action, the relevance of the end point data to carcinogenicity, the number of studies of each end point, the consistency of results in different test systems and different species, and the concordance of dose-response relations for tumor and mode of action-related end point data should be considered in developing a conclusion. It is this mode of action conclusion that drives the dose-response assessment.

5.6. Variation in human susceptibility to carcinogenesis

The 1996 guidelines call for consideration of the effects of carcinogens on subpopulations of human beings who may be at an elevated risk for cancer. Human variation in response to carcinogenic exposures is a complex process that is most likely mediated by a number of mechanisms, including polymorphisms in genes involved in metabolism and DNA repair (Williams et al., 1996). There are a number of biomarkers of genetic (e.g., changes in proto-oncogenes and tumor suppressor genes, polymorphisms in genes for metabolizing enzymes, as well as levels of DNA adducts, sentinel mutations, chromosomal aberrations) or biological (e.g., hor-

monal levels) events that can be measured in humans that may help to identify sensitive or high risk subpopulations.

5.7. Dose-response assessment

The soundness of the final inferences concerning human risk depends on the plausibility of the extrapolations that are necessary. Under the proposed guidelines, the understanding of the underlying biological mechanisms as they vary from species to species, from high dose to low dose, and from one route of exposure to another is applied to enhance this plausibility. Knowledge of the mechanisms underlying the induction of tumors can help reduce the uncertainties attendant to the inferential process of risk analysis. Thus, in the 1996 proposed guidelines, the dose-response extrapolation procedure follows conclusions about mode of action in the hazard assessment. The term 'mode of action' is deliberately chosen in the new guidelines in lieu of 'mechanism' to indicate using knowledge that is sufficient to draw a reasonable working conclusion without having to know the processes in detail as the term 'mechanism' might imply.

5.8. The range of observation

The dose-response assessment under the new guidelines is a two-step process. In the first step, the response data are modeled in the range of empirical observation. Modeling in the observed range is done with biologically based or appropriate curve-fitting modeling. The second step, extrapolation below the range of observation is accomplished by modeling if there are sufficient data or by a default procedure. A point of departure for extrapolation is estimated from modeling observed data. The lower 95% confidence limit on a dose associated with 10% extra risk (LED_{10}) is proposed as a standard point of departure. The 10% response is at or near the limit of sensitivity in most cancer bioassays (and epidemiology studies). Other points of departure may be appropriate, e.g., if a response is observed below the 10% level. Some data sets (e.g., certain continuous data) may not be amenable to curve-fitting and choosing a point of departure but to estimation of a low- or no-observable-adverse-effect level.

5.9. Modeling of nontumor data

The proposed guidelines allow for the opportunity to model not only tumor data but other responses thought to be important precursor events in the carcinogenic process (e.g., DNA adducts, mutation, chromosomal translocations or deletions, aneuploidy, cellular proliferation, hormonal or physiological disturbances, receptor binding). The modeling of important precursor response data makes extrapolation based on default procedures (discussed below) more meaningful by providing insights into the relationships of exposure and tumor response below the observable range. Additionally, modeling of nontumor data may provide support for selecting a certain extrapolation procedure (linear versus nonlinear). If the nontumor end point is believed to be part of a continuum that leads to tumors, such data could be used to extend the dose-response curve below the observed tumor response or modeled with the tumor data as an integrated data set. If the nontumor response is believed to be an obligatory step in the carcinogenic process or is considered to be more informative of the agent's carcinogenicity, then it may be modeled and used for extrapolation instead of the available tumor data.

5.10. The range of extrapolation: default approaches

The proposed guidelines indicate a preference for biologically based dose-response models, such as the two-stage model of initiation plus clonal expansion and progression (Chen and Farland, 1991), or case-specific dose-response models for the extrapolation of risk. Because the parameters of these models require extensive data, it is anticipated that the necessary data to support these models will not be available for most chemicals. Therefore, the 1996 proposed guidelines allow the use of several default extrapolation approaches based on mode of action information about the agent.

5.11. Linear default extrapolation procedure

The LMS procedure of the 1986 guidelines for extrapolating risk from upper-bound confidence intervals is no longer recommended as the linear default in the 1996 proposed guidelines. The linear

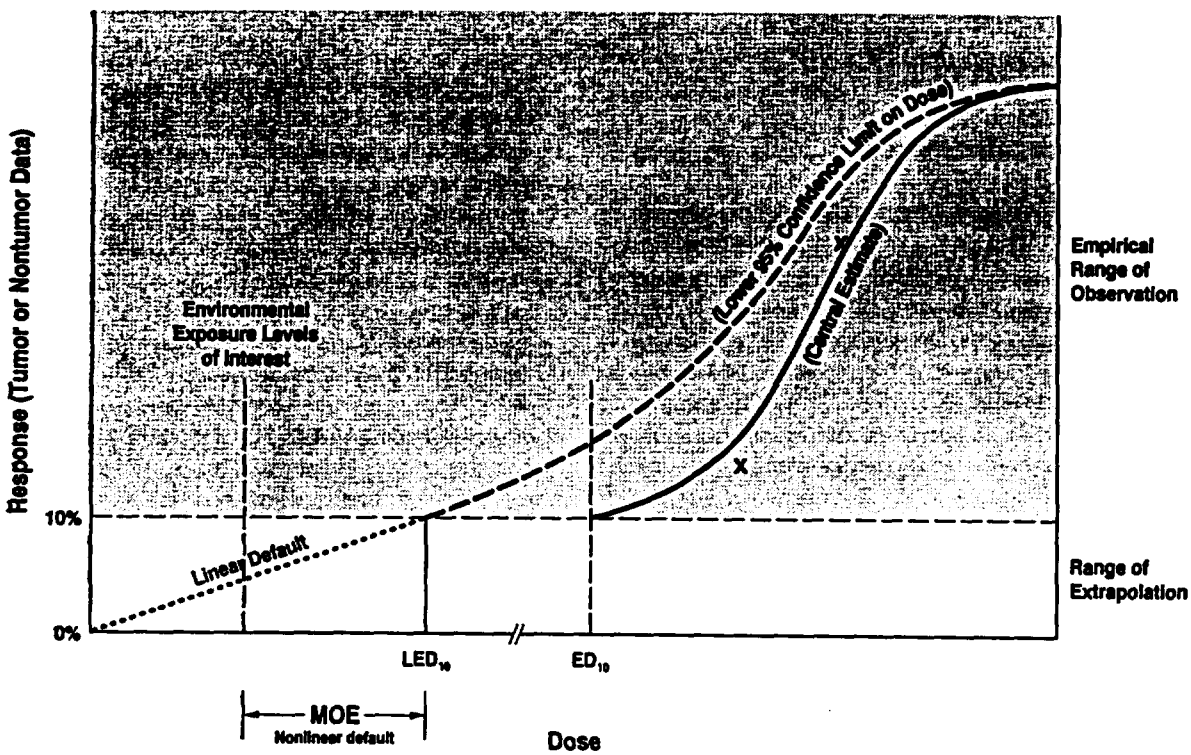

Fig. 4. The dose-response (DR) assessment of the USEPA 1996 *Proposed Guidelines for Carcinogen Risk Assessment*. DR is a two-step process; in the first step, response data are modeled in the range of observation, and the point of departure below the range of observation is determined. The LED_{10} (effective dose corresponding to the lower 95% limit on a dose associated with 10% response) is used as a point of departure for the second step of extrapolation to the origin as the linear default or for a margin of exposure discussion as the nonlinear default. The LED_{10} is the standard point of departure, but another may be used if more reasonable, given the data set.

default in the new guidelines is a straight-line extrapolation to the origin from the point of departure (LED_{10}) identified in the range of observed data (Fig. 4). It should be noted that the straight-line extrapolation from the LED_{10} and the LMS procedure produce similar results (Gaylor and Kodell, 1980). The straight-line/LED_{10} approach does not imply unfounded sophistication as extrapolation with the LMS procedure does.

The linear default approach would be considered for agents that directly affect growth control at the DNA level (e.g., carcinogens that directly interact with DNA and produce mutations). There might be modes of action other than DNA reactivity (e.g., certain receptor-based mechanisms) that are better supported by the assumption of linearity. When inadequate or no information exists to explain the carcinogenic mode of action of an agent, the linear default approach would be used as a science policy choice in the interest of public health. Likewise, a linear default would be used if evidence demonstrates the lack of support for linearity (e.g., negative genotoxicity studies), but there is also an absence of sufficient information on another mode of action to explain the induced tumor response. The latter is also a public health conservative policy choice.

5.12. Nonlinear default extrapolation procedure

Although the understanding of the mechanisms of induced carcinogenesis likely will never be complete for most agents, there are situations where evidence is sufficient to support an assumption of nonlinearity. Because it is experimentally difficult to distinguish modes of actions with true 'thresholds' from others with a nonlinear dose-response relationship, the pro-

posed nonlinear default procedure is considered a practical approach to use without the necessity of distinguishing sources of nonlinearity.

In the 1996 proposed guidelines, the nonlinear default approach begins at the identified point of departure (LED_{10}) and provides a margin of exposure (MOE) analysis rather than estimating the probability of effects at low doses (Fig. 4). The MOE analysis is used to compare the LED_{10} with the human exposure levels of interest. The MOE is the LED_{10} (or other point of departure) divided by the environmental exposure of interest. The key objective of the MOE analysis is to describe for the risk manager how rapidly response may decline with dose. Thus, the MOE analysis considers the steepness of the slope of the dose response along with information on such factors as human differences in sensitivity, interspecies differences, nature of response being used for point of departure (i.e., tumor or nontumor data), and biopersistence of the agent.

A nonlinear default position must be consistent with the understanding of the agent's mode of action in causing tumors. For example, a nonlinear default approach would be taken for agent's causing tumors as a secondary consequence of organ toxicity or induced physiological disturbances. Because there must be a sufficient understanding of the agent's mode of action to take the nonlinear default position, it is anticipated that the modeling of precursor responses to tumor development will play an important role in providing support for nonlinearity, or be used instead of tumor data for determining the point of departure for the MOE analysis.

5.13. Both linear and nonlinear defaults

There may be situations where it is appropriate to consider both linear and nonlinear default procedures. For example, an agent may produce tumors at multiple sites by different mechanisms. If it is apparent that an agent is both DNA reactive and highly active as a promoter at higher doses, both linear and nonlinear default procedures may be used to distinguish between the events operative at different portions of the dose-response curve and to consider the contribution of both phenomena.

5.14. Risk characterization

Risk assessment is an integrative process that culminates ultimately into a risk characterization summary. Risk characterization is the final step of the risk assessment process where all preceding analyses (i.e., from hazard assessment, dose-response assessment, and exposure assessment) are tied together to convey the overall conclusions about potential human risk (Fig. 2). This component of the risk assessment process produces a summary that characterizes the data in nontechnical terms, explaining the key issues and conclusions of each component of the risk assessment and the strengths and weaknesses of the data. Because risk characterization is the product of risk assessment used in risk management decisions, it needs to be much more than a number and a letter category of human cancer risk. Thus, the 1996 proposed guidelines describe what should be contained in a risk characterization summary and how it should be presented.

6. Conclusion

Compared with the 1986 guidelines, the revised guidelines call for a more complete discussion of the issues and an evaluation of all relevant information. These guidelines promote the use of mode of action information in cancer risk assessment to reduce the uncertainties associated with using experimental data to characterize and project how human beings will respond to certain exposure conditions. Given this emphasis on mechanisms, it is hoped that these guidelines will promote research and testing to improve the scientific basis of cancer risk assessment and stimulate thinking on how such information can be applied.

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